ETIOLOGIES OF PSEUDORETINOBLASTOMAS IN HISTOPATHOLOGIC SPECIEMENS OF ENUCLEATED OR EXENTERATED EYES WITH CLINICAL DIAGNOSIS OF RETINOBLASTOMA

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Abstract- Retinoblastoma is the most common primary intraocular malignancy in childhood. Enucleation remains the treatment of choice in many children because the eye can not be salvaged with any other treatment modality. In some cases after enucleation etiologies other than retinoblastoma are detected in histopathologic review (pseudoretinoblastomas). This study aims to evaluate the prevalence and etiologies of pseudoretinoblastomas in those eyes enucleated or exenterated due to clinical and radiological diagnosis of retinoblastoma in Farabi Hospital from April 1986 through February 2000. Records of all 453 patients who had sustained enucleation or exenteration due to diagnosis of retinoblastoma during these 15 years were reviewed for reports of histopathologic specimens. In those cases where the histopathologic reports were not consistent with retinoblastoma, Hematoxylin & Eosin stained slides were studied again. Histological diagnosis of retinoblastoma was confirmed in 400 cases (88.3%), and 53 cases were pseudoretinoblastomas (11.7%). This frequency was in agreement with previous studies. Most common etiologies of pseudoretinoblastomas were endophthalmitis (22.7%), phthisis bulbi, vitreous hemorrhage and retinal detachment (17% each) and coat's disease (11.3%).
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INTRODUCTION

Retinoblastoma is the most common intraocular tumor of childhood and the most common tumor of the retina (1). Being responsible for 1% of all cancer deaths from birth to 15, it warrants accurate diagnosis and prompt treatment. Leukocoria is the most common presenting sign of retinoblastoma which is seen in 60% of cases (2). However a number of benign conditions can sometimes clinically simulate retinoblastoma and present with leukocoria or other signs, often creating diagnostic difficulty for the ophthalmologist. These are called "pseudoretinoblastomas" and as their management considerably differs from that of retinoblastomas, their accurate diagnosis is mandatory. Until recently, many eyes with pseudoretinoblastomas were enucleated with the erroneous diagnosis of retinoblastoma. One report in 1962 by Kogan *et al.* revealed an error rate of 30% in eyes enucleated for suspected retinoblastoma (3). In other series error rates of 27% and 16% were reported for enucleation of pseudorerinblastomas (4,5). In academic centers of Western countries, 10-15% and even 20% of enucleated eyes for suspected retinoblastomas were proved to be pseudoretinoblastomas and it is said that this rate is rather unavoidable (1, 2). In nonacademic centers, diagnostic error of even up to 50% has been reported (1). The most common causes of leukocoria other than retinoblastoma are coat's disease, ocular

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toxocariasis, primary hyperplastic persistent vitreous (PHPV) and retinopathy of prematurity, and the first three account for approximately 60% of pseudoretinoblastomas (1).

In a large study in 1991 by Shields *et al.* the most common etiologies of pseudoretino-blastomas in order of frequency were PHPV (28%), Coat's disease (16%), and toxocariasis (16%) (6,7). Accordingly, accurate diagnosis of this entity can save the child from permanent eye enucleation and its psychological effect. Even if the eye is not functional for the patient, it's apparent being has considerable psychological effect for the patient and his/her parents and his future social and individual function. This study aims to reveal the prevalence and etiologies of pseudoretinoblastomas in histopathologic specimens of enucleated or exentrated eyes with clinical and radiological diagnosis of retinoblastoma in Farabi Hospital, Tehran.

MATERIALS AND METHODS

Histopathological records of all 453 patients diagnosed clinically and radiologically as retinoblastoma from April 1986 through February 2000 were reviewed retrospectively in Farabi Hospital pathology department, Tehran, Iran. The study period was between April 1986 to the end of February 2000. In those cases where the histopathologic report was not consistant with retinoblastoma (pseudoretino-blastoma), H&E stained slides were reviewed again.

SPSS software (version 10) was used for data entry and analysis. $P = 0.05$ was considered as the level of significance (Standard t test and Chi square were used for statistical analysis).

RESULTS

Among studied cases, 400 proved to be retinoblastoma (88.3%) and 53 cases were pseudoretinoblastomas (11.7%). In 400 retinoblas-toms, 239 were male (59.8%) and 161 were female (40.3%), and in 53 pseudoretinoblastomas, 35 were male (66%) and 18 were female (34%) (Table 1).

In retinoblastoma group, right eye was involved in 181 (45.3%) and left eye was involved in 212 cases (53.3%). In 50 cases, both eyes were involved (1.4%) (Table 1). In 7 cases, the side of involved eye was not indicated in the records. In 53 cases of pseudoretinoblastoma, right eye was involved in 26 cases (49%), left eye in 26 cases (49%), and we had 1 missing case (Table 1). Mean age and standard deviation (SD) of patients in total dataset was 34.6±25.9 months with a minimum of 15 days and maximum of 14 years. Mean age and of patients who proved to have retinoblastomas was 32.23±23 months with the range of 1-120 months. Mean age and SD in pseudoretinoblastoma group was 44.8±40.5 months with the range of 0.5-168 m. There was a significant difference between the mean age of retinoblastoma and pseudoretinoblastoma groups ($P = 0.047$) with mean age of pseudoretinoblastoma patients being higher than that of retinoblastoma patients. Table 2 shows age in retinoblastoma and pseudoretinoblastoma groups according to sex. There was no significant difference between the two groups on gender and side of eye involvement.

Etiologies detected after reviewing the H&E stained slides of pseudoretinoblastomas in our ophthalmic pathology department are shown in table 3. Among cases with endophthalmitis, 6 were chronic, 3 were acute and 3 cases were accompanied with intraocular hemorrhage. As it is evident from the table, the sum of detected etiologies (n=61) outnumber relevant cases (n=53), as in some cases more than one pathology were detected.

Table 1. Frequency distribution of sex and side of involved eye in histopathologic speciemens of enucleated eyes

Variable	Retinoblastoma (n= 400)	Pseudoretinaoblastoma (n= 53)
Sex		
Male	239 (59.8)	35 (66)
Female	161 (40.3)	18 (34)
Involved eye		
Right	181 (45.3)	26 (49.1)
Left	212 (53.31)	26 (49.1)
Bilateral	50 (1.4)	0 (0)

*Data are given as number (percent).

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Table 2. Mean age, SD and range of age in retinoblastoma and pseudoretinoblastoma groups in males and females

	Range of age*	**Mean age***	**SD**	***P* Value**
Retinoblastoma				
Male (n= 239)	1.5-120	32.33	23	$t = -0.95$
Female (n= 160)	1-120	34.57	22.58	$P = 0.78$
Pseudoretinoblastoma				
Male (n= 35)	0.5-120	42.58	30.3	$t = -0.45$
Female (n= 18)	3-168	49.028	56.24	$P = 0.655$

Abbreviation: SD, standard deviation.

* Month.

The most common presenting signs of retinoblastoma and pseudoretinoblastoma was also reviewed as follow: leukocoria, strabismus, red eye, proptosis, decreased visual acuity, photophobia and orbital mass. Among 277 cases in retinoblastoma group with nonmissing data on presenting signs, 222 had presented with leukocoria (80.1%), 22 with strabismus (7.9%), 30 with red eye (10.8%), 36 with proptosis (12.9%) and 3 cases with decreased visual acuity (1%).

In some patients two presenting signs occurred simultaneously and each was categorized separately (Table 4). Similarly, among 31 cases of pseudoretino-blastomas, 22 had presented with leukocoria (70.96%), 9 with strabismus (29%), 5 with red eye (16.1%), 3 with proptosis (9.6%), 3 with decreased visual acuity (9.6%), 1 with photophobia (3.2%) and one case with orbital mass (3.2%) (Table 4).

Table 3. Frequency etiologies of pseudoretinoblastomas in histopathologic specimens of enucleated eyes

Pseudoretinoblastoma etiologies	Number	Percent
Endophthalmitis	12	22.7
Vit. Hemorrhage	9	17
Retinal detachment	9	17
Phthisis bulbi	9	17
Coat's disease	6	11.3
PHPV	4	7.5
Retinal dysplasia	4	7.5
Rhabdomyosarcoma	3	5.7
Retinal angiomatosis	1	1.9
Cataract	1	1.9
Congenital anomaly	1	1.9
Iridocyclitis	1	1.9
Diffuse retinal gliosis	1	1.9
Total	61	100

Leukocoria as a presenting sign was more commonly detected in retinoblastoma than in pseudoretinoblastoma patients ($P = 0.012$). On the other hand strabismus was more frequently detected in pseudo-retinoblastoma than in retinoblastoma group ($P = 0.001$). No significant difference was observed in frequency of red eye or proptosis between the two groups.

The frequency of decreased visual acuity, photophobia, and orbital mass were also higher in pseudoretinoblastoma group ($P = 0.002$, $P = 0.005$ and $P = 0.005$, respectively). Frequency distribution of presenting signs according to sex in each clinical group is demonstrated in table 4.

DISCUSSION

In our study, retinoblastoma and pseudoretino-blastomas were confirmed in 400 cases (88.3%) and 53 cases (11.7%), respectively. According to previous studies by Kogen *et al.* in 1962 (3) and Robertson *et al.* in 1977 (5), who reported diagnostic errors of 30% and 16% and another study by Margo *et al.* who reported 27% diagnostic pitfall(4), our results were unavoidable and within an acceptable range. An interesting point in our study was difference in mean age between the two groups.

Mean age in retinoblastoma group was 33.23 months and in pseudoretinoblastoma group was 44.77 months ($P = 0.04$). This means that in older children suspected to have retinoblastoma it is better to think of pseudoretinoblstoma etiologies as well and perform other complementary diagnostic tests such as vitreous aspiration and cytologic evaluation before doing enucleation in order to reduce the number of diagnostic errors.

Table 4. Frequency distribution of presenting signs according to sex in each clinical group

Presenting sign	Retinoblastoma (n= 277)			Pseudoretinoblastoma (n= 31)		
	Male	Female	Total	Male	Female	Total
Leukocoria (n= 244)	133 (48%)	89 (32.1%)	222 (80.1%)	16 (51.6%)	6 (19.35%)	22 (70.96%)
Strabismus(n= 31)	16 (5.7%)	6 (2.1%)	22 (7.9%)	7 (22.58%)	2 (6.4%)	9 (29%)
Red eye (n= 35)	16 (5.7%)	14 (4.9%)	30 (10.8%)	5 (16.1%)	0 (0%)	5 (16.1%)
Proptosis (n= 39)	22 (7.9%)	14 (5%)	36 (12.9%)	2 (6.4%)	1 (3.2%)	3 (9.6%)
Reduced visual acuity (n= 6)	1 (0.3%)	2 (0.7%)	3 (1%)	1 (3.2%)	2 (6.4%)	3 (9.6%)
Photophobia (n= 1)	0 (0%)	0 (0%)	0 (0%)	1 (3.2%)	0 (0%)	1 (3.2%)
Orbital mass (n= 1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.2%)	1 (3.2%)

* Data are given as number (percent).

We found differences in pseudoretinoblastoma etiologies in comparison with previous studies: the most common etiology in our setting was endophthalmitis which accounted for 22.7% of cases. It's probable that in some cases there had been some previous trauma in the child occurring without notice of parents/carers; thus without any history of trauma, retinoblastoma diagnosis had been suggested. In a study by Balmer *et al.* in 1988 the most common etiology of pseudoretinoblastoma was coat's disease (8). In the report by Shields *et al.* PHPV (28%), coat's disease (16%) and ocular toxocariasis (16%) were the most common etiologies in order of frequency (6,7). The three next common etiologies of pseudoretinoblastoma in our study were phthisis bulbi, vitreous hemorrhage and retinal detachment, each accounting for 17%. Phthisis bulbi is an end stage disorganized eye where all its structures are distorted and can be the last fate of a tumor like retinoblastoma, so we don't elaborate on it in this article. As diagnosis of pseudoretinoblastoma is a clinico-pathologic one, in cases of having more accurate histories of the patients, we may have been able to classify those with vitreous hemorrhage and retinal detachment in the group of congenital lesions or others, because these findings are seen in the pathology specimen of many lesions such as PHPV, retinal dysplasia and so on. Some of the differences between our results and other reports can be attributable to missing data in patients records and this might be the most important limitation of our study. After the above 4 etiologies there were coat's disease (11.3%), PHPV (7.5%) and retinal dysplasia (7.5%). Interestingly, there were 3 cases of rhabdomyosarcoma (5.7%). It seems that some patients were admitted in the very advanced stage of disease and in that stage, differentiation of rhabdomyosarcoma from retinoblastoma had been difficult due to tumoral extension. Other rarer etiologies were angiomatosis retinae (1.9%), cataract (1.9%), congenital anomaly (not specified) (1.9%), iridocyclitis and chorioretinitis (1.9%) and diffuse retinal gliosis (1.9%). Prevalence of these etiologies were almost similar to previous studies (6). The fourth common etiology in Western studies was retinopathy of prematurity (ROP) (1,6,7). In our study in Farabi Hospital we neither had any cases of ROP nor any documented toxocariasis. Lack of ROPs in our setting might be attributable to familiarity of physicians in the recent years with this entity in premature infants that has led to intensive screening programs, early diagnosis and treatment, and the previously high mortality in these cases in our country. In epidemiologic studies dogs are the chief culprits in spreading toxocariasis (9) and in Iran, it's not customary in families to keep puppies; this may have led to lack of any documented toxocariasis among our dataset. As mentioned previously, our study was a retrospective histopathologic one and we couldn't do paraclinical tests such as ELISA or the better IFA for diagnosing toxocariasis. As the most common histopathologic finding in enucleated eyes with toxocara endophthalmitis is chronic sclerosing vitritis with predominance of plasma cells and eosinophils (1), may be some of those cases defined as chronic endophthalmitis in our study have had toxocariasis but we had no documented data.

In considering the presenting signs in our setting,

leukocoria was significantly more prevalent among cases with retinoblastoma than pseudoretinoblastoma (P = 0.012) and in pseudoretinoblastoma group, strabismus was significantly more than retinoblastoma group (P = 0.001); so in patients presenting with strabismus and suspected to have retinoblastoma, it is wise to examine the patients more accurately and even do more diagnostic tests in order to decrease diagnostic error. In a study by Abramson *et al.,* the most common presenting signs of retinoblastoma were leukocoria (56.1%) and then strabismus (23.6%) (10). It goes without saying that not all those presenting with leukocoria have retinoblastoma. At last it may be better to do anterior chamber and vitreous tap for cytology in the most suspicious cases of retinoblastoma before doing any treatment modality to reduce diagnostic error and its implicated outcomes (6). Prospective studies in the future can be of greater help to depict the characteristics of pseudoretinoblstomas more precisely.

Acknowledgement

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